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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/021,955
Filing Date: December 13, 2001
Appellant(s): LUPSKI ET AL.

Mellissa L. Sistrunk
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed June 13, 2005.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The rejection of claims 1-7, 35-40, 42-61 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

No prior art is relied upon by the examiner in the rejection of the claims under appeal.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 35-40 and 42-61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue (see In re Wands, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include, but are not limited to:

Quantity of Experimentation Necessary

Amount of Direction and Guidance

Presence and Absence of Working Examples

Nature of Invention

Level of Predictability and unpredictability in the art

Nature of the Invention :

Claims 1-7 are drawn to a method of diagnosing myelinopathy in an individual and claims 35-40, and 42 are drawn to a method of detecting the presence or absence of any mutation in a periaxin polynucleotide and its association with any myelinopathy. Further, Claim 7 is drawn to a specific alteration in a periaxin polynucleotide and Claim 36 is drawn to an association between a specific mutation in periaxin and any myelinopathy. Claims 4 and 40 are broadly drawn to a broad range of diseases of myelinopathy such as Charcot-Marie-Tooth (CMT) syndrome, hereditary neuropathy with liability to pressure palsies (HNPP), Dejerine-Sottas syndrome (DSS), congenital hypomyelinating neuropathy (CHN), and Roussy-Levy syndrome (RLS). Claim 50 is drawn to a DSS. Claim 58 drawn to a prominent sensory neuropathy. Claims 53-56 are drawn to a method of identifying alteration comprising homozygous, heterozygous and compound heterozygous periaxin mutations. Claims 57 and 61 are drawn to a method of identifying an individual suspected of having myelinopathy or being a carrier of myelinopathy.

Amount of Direction and Guidance:

The specification discloses the identity of several mutations in periaxin polynucleotide and their locations (see Figs. 4 and 9). The specification on page 14, asserts a correlation between the human orthologue of murine and rat periaxin (PRX) with human inherited myelinopathy and further asserts that human periaxin gene which encodes two PDZ domain proteins, is required for the maintenance of peripheral nerve myelin. The specification teaches that based on knockout animal models, periaxin is correlated to the proper formation of myelin sheaths and the specification broadly discloses the identification of recessive PRX mutations comprising nonsense and frame shift mutations in the periaxin gene. The specification asserts that based on the common known methods in the art, mutations in other periaxin polynucleotide sequences (for

example SEQ ID No. 76) could be detected. The specification discloses mutations in SEQ ID No.1 and extrapolates the use of similar techniques to detect mutations in other periaxin polynucleotides (for example SEQ ID NO.76). The specification discloses mutations in other genes associated with some myelinopathy (see page 20) (such as DNA rearrangements in CMT patients caused by mutations in MPZ, Cx32, EGR2, and mutations in MPZ and EGR2 in DSS patients). Further the specification on page 21, asserts the function of periaxin in the maintenance of the myelin sheath based on animal studies. However, the specification has not established that a statistically significant association exists between all of the specific mutations disclosed in the specification, and any myelinopathy, or any specific myelinopathy, or that a predictable correlation can be made as to an association between any mutation in the periaxin gene and any myelinopathy or any specific myelinopathy. Further the specification has not established that any periaxin mutation is associated with DSN and no predictable correlation is established that any homozygous periaxin mutation or that two different mutations in a compound heterozygote are associated with myelinopathy in general. With regard to the new claims 51-61, the specification (on page 65, example 3) provides evidence for compound heterozygous with a deletion and a transition mutation associated with specific types of myelinopathies that is one form of CMT and DSN. However, the specification fails to establish that any alteration in PRX is diagnostic for myelinopathy in general, nor that the presence of a single mutation in a single allele would indicate that someone is susceptible to myelinopathy or a carrier of a periaxin associated myelinopathy as it is clear that mutations in PRX exist which are not only not diagnostic but also not associated with myelinopathy (table 2). The specification exemplifies that the presence of an

alteration in the periaxin gene is not necessarily diagnostic for myelinopathies or an indicator that someone is a carrier for a disease causing mutation, as broadly claimed.

Presence and Absence of working examples:

The specification discloses a method of screening Prx mutations in some family studies and detected mutations comprising a deletion and a transition in the affected patients with peripheral neuropathy. The specification correlates the mutations with the loss of function of PRX gene in relation to studies in rat (example 4). The examples 2-4 in the specification establish a positive correlation between the presence of a periaxin polynucleotide comprising mutation which results in a truncated periaxin polypeptide in patients with undisclosed myelinopathy, wherein said patients have two aberrant forms of periaxin polypeptides. Although the specification does not demonstrate any alteration in PRX is associated with myelinopathies in general, the specification asserts that the mutations could be associated with loss of function of the periaxin polypeptide. It is noted, however, that these examples also establish that the mere presence of a mutation (i.e., only a single copy) is NOT associated with the disease as in HOU579 family, wherein the unaffected parents had an allele with single mutated PRX polynucleotide and another allele of wild type PRX polynucleotide. Further there is no description of the type of peripheral neuropathy of the affected patients. (see page 65, example 3). Further examples in the specification merely asserts correlation between mutations in PRX with myelinopathy in general, however no specific mutation is associated with any of the different types of myelinopathies as exemplified by the example 8 in the specification (see page 72). Further Table- 2 shows that the unaffected control subjects contain mutations in periaxin. The specification does not teach whether the mutations in Table-2 are associated with loss of function or if they are statistically

associated with any specific peripheral neuropathy or any specific myelinopathy. Thus the mere detection of an alteration in PRX gene is not diagnostic for myelinopathies in general. The specification fails to show that all alterations are diagnostic or associated with myelinopathies because the specification shows that carriers having an alteration are unaffected with myelinopathy (Table-2). Thus all carriers having an alteration or mutation in PRX would not be carriers of disease-causing PRX mutations. The specification does not provide guidance as to which PRX alterations are predictably associated with myelinopathy in general, or not associated with myelinopathy. Further the specification does not provide guidance as to which PRX alterations would indicate an individual being a carrier of disease-causing mutations or not.

Level of Predictability and unpredictability in the art :

Predictability in the art suggests mutations in genes other than the specific periaxin gene, are associated with specific type of myelinopathy, for example Boss et al. (USPN. 5,691,144) teaches mutations in connexin-32 are associated with X-linked Charcot-Marie-Tooth (CMT) disease, Timmermann et al. (Neurology, Vol. 52, pp. 1827-1832, 1999) teach a missense mutation in EGR2 gene in association with Dejerine-Scottas syndrome (DSS). Lupski et al. (USPN. 5,780,223) teach DNA duplication in CMT1A gene sequence association with autosomal dominant CMT disease, and Roa et al. (Nature Genetics, Vol. 5, pp. 269273, 1993) teach that some point mutations in peripheral myelin protein 22 (PMP22) gene are associated with CMT1A, while others are associated with DSS (Fig.3, page 271). With regards to the specific periaxin gene Guilbot et al. (Human Molecular Genetics, Vol. 10, No.4, 2001), teach periaxin is responsible for CMT4F, an autosomal recessive form of CMT disease, and Gillepsie et al. (Neuron, Vol. 12, pp. 497-508, 1994) teach role of periaxin in rat peripheral nervous

system and discloses that periaxin localization in schwann cells and its possible role in ensheathment. Further, Takashima et al. disclose periaxin mutations cause a broad spectrum of demyelinating neuropathies and disclose that affected patients with CMT or DSN comprise PRX mutations in homozygous condition, that is both alleles are mutated with a specific mutation and the unaffected family members are carriers for myelinopathy, that is a single allele of PRX is mutated (Takashima et al. Ann. Neurol., Vol. 51, pp. 709-715, 2002). Kijima et al. disclose yet another Prx mutation causing early-onset but slow-progressive CMT disease (Kijima et al. J Hum Genet., Vol. 49, pp. 376-379, 2004). However, the art does not establish a predictable association that any specific mutation in periaxin or any other genes is predictably associated with all of the large number of diseases encompassed by the recitation of "myelinopathy". For example Roa et al. teach that while some point mutations in PMP22 are associated with CMT1A, others are associated with DSS. Further, while Boerkoel et al. (Am. J. Hum. Genet., Vol. 68, pages 325-333, 2001) teach that certain specific mutations are associated with DSN, when both copies of periaxin gene are altered, Boerkoel et al. further teach that the family members with only one altered copy of periaxin gene were not affected and also teach a number of missense mutations in normal and unaffected family members. Further, Takashima et al. teach similar study, wherein DSN or CMT affected patients have two mutated alleles where as the unaffected have one mutated allele with no demyelination. The art is further silent with regard to a predictable association between any specific alteration or mutation in periaxin and a representative number of diseases encompassed by the term "myelinopathy". Diseases encompassed by the term "myelinopathy" include a large number of heterogeneous diseases with differing symptoms and associations to genetic mutations. To date, however, there is no evidence

that the association of an alteration or mutation in a specific gene and a specific form of myelinopathy can predictably correlate the presence of any other, or all, specific myelinopathy encompassed by the broad term "myelinopathy". The claims further broadly encompass detecting an association between any specific mutation in periaxin, and an association to a specific unnamed myelinopathy. The specification, however does not establish a statistically significant association with any of the disclosed mutations in periaxin, and any specific form of myelinopathy such that the skilled artisan might be able to predictably correlate which mutations in periaxin would be associated with a specific form of myelinopathy. The mere detection of an alteration in PRX gene is not associated with myelinopathies in general. Further, to date, no teaching is available in the art with regards to a universal correlation between any mutation in periaxin and an association with any general or specific type of myelinopathy. It is apparent from the prior art that the unpredictability is high and the instant specification fails to teach any particular mutation associated with any particular type of myelinopathy. Given the broad scope of the claims, the specification does not provide any specific example that would easily predict a significant association of any particular mutation in periaxin with any particular type of myelinopathy. Further, CMT is inherited in three forms, i.e., autosomal dominant, autosomal recessive and X-linked conditions. The specification fails to support an association of a mutation in periaxin with all the three forms of CMT.

In addition, the specification does not establish the identity of any specific critical nucleotide or amino acid alteration(s) that are associated with loss of function or are associated with myelinopathy. The missense mutations in Table-2 were also found in unaffected controls. The specification does not teach if patients had one copy of mutation, or if they were homozygous or

compound heterozygous for other mutations in periaxin. It is clear from the teachings in Table-2, that the mere presence of an alteration in periaxin such as a substitution or deletion is not indicative of myelinopathy. Further, with regard to the 2145T-> A and 274Δ C mutation in claim 36, and the R196X, C715X, or R82FSX96, the specification has provided no data as to whether these mutations are even associated with myelinopathy. Since the specification has not identified any specific critical amino acid alteration, it is further unclear whether these mutations or any specific mutation will have a significant affect or not. With regard to the heterozygous carriers carrying a PRX mutant allele, the specification fails to establish that the mere presence of an alteration in PRX as claimed broadly in the new claims 51-61 would result in carriers of disease causing PRX mutant alleles, or result in susceptibility to any myelinopathy.

Quantity of Experimentation Necessary:

Given the lack of guidance in the specification and the unpredictability in the art, it would require a large amount of experimentation to practice the invention as claimed. Neither the art nor the specification provides the skilled artisan with a predictable correlation that any mutation in periaxin is significantly associated with any specific myelinopathy. To practice the invention as claimed, the skilled artisan would have to perform a large study of patients with different types of myelinopathy, such as CMT, DSS, and matched controls to determine if any general alteration or mutation in periaxin or any specific claimed alteration or mutation in peraxin, was associated with any myelinopathy in general. Such a study would consist of mainly trial and error analysis, the outcome of which is clearly unpredictable as exemplified by the state of the art. Further, it would require a large amount of experimentation to distinguish, which PRX mutant allele carriers are associated with the myelinopathy in general or which PRX mutant

allele carriers are not associated with myelinopathy. Thus a mere presence of an alteration is not diagnostic for any myelinopathy or is not diagnostic for identifying a carrier having a disease-causing PRX mutant allele. Therefore, given the lack of guidance from the specification as to any statistical association between the claimed association of any mutation in peraxin polynucleotide and any myelinopathy, and the unpredictability taught in the art as to some point mutations in other genes such as PMP22 are associated with one form of CMT, while other mutations in the same PMP22 are associated with DSS, the skilled artisan would be required to perform undue experimentation to practice the invention as broadly as it is claimed.

(11) Response to Arguments:

The instant claims 1-7 are drawn to a method of diagnosing myelinopathy in an individual and claims 35-40, and 42 are drawn to a method of detecting the presence or absence of any mutation in a periaxin polynucleotide and its association with any myelinopathy. Further, Claim 7 is drawn to a specific alteration in a periaxin polynucleotide and Claim 36 is drawn to an association between a specific mutation in periaxin and any myelinopathy. Claims 4 and 40 are broadly drawn to a broad range of diseases of myelinopathy such as Charcot-Marie-Tooth (CMT) syndrome, hereditary neuropathy with liability to pressure palsies (HNPP), Dejerine-Sottas syndrome (DSS), congenital hypomyelinating neuropathy (CHN), and Roussy-Levy syndrome (RLS). Claim 50 is drawn to a DSS. Claim 58 drawn to a prominent sensory neuropathy. Claims 53-56 are drawn to a method of identifying alteration comprising homozygous, heterozygous and compound heterozygous periaxin mutations. Claims 57 and 61 are drawn to a method of identifying an individual suspected of having myelinopathy or being a carrier of myelinopathy.

On page 5 of the appeal brief, Appellants argue that the specification is enabled to one skilled in the art to make and use the invention as claimed. On page 6-7 of the brief, Appellants address the standard for enablement under 35 USC 112, first paragraph, and argue that the instant specification meets the standard as determined by the courts, and the instant specification provides considerable amount of routine experimentation and reasonable amount of guidance and working examples and asserts that the section 112 requires simply that the patent applicant provide a disclosure which sufficiently enables one skilled in the art to carry out the invention commensurate with the scope of the claims. Appellants' arguments are fully considered and found unpersuasive. The instant claims broadly recite diagnosing myelinopathy, which comprises a wide range of myelinopathies and are not limited to any one type of myelinopathy. Further the instant claims require the skilled artisan to assay each possible periaxin (PRX) alteration (mutation or polymorphism), to determine which are associated with the myelinopathy in general. This leads to further experimentation to determine which mutations are associated with which type of myelinopathy.

With regard to the Appellants' assertions on page 8-9 of the appeal brief, that the instant specification provides reasonable amount of guidance and working examples, and undue experimentation is not required, the arguments are fully considered and are found unpersuasive. It is noted that all the claims require diagnosis resulting from the detection of an alteration in PRX, but the specification does not provide a predictable correlation that the mere presence of an alteration in PRX would predict an association with myelinopathy in general, be diagnostic of myelinopathy in general, or any specific myelinopathy. In fact, the specification provides evidence that the mere presence of a mutation (i.e., only a single copy) is NOT diagnostic of

disease as in HOU579 family, wherein the unaffected parents (hyterozygous carriers) had an allele with single mutated PRX polynucleotide and another allele of wild type PRX polynucleotide (see page 65, example 3). In Table 2, the specification further provides evidence that the mere presence of an alteration in PRX is neither diagnostic for nor associated with myelinopathy in general nor any specific myelinopathies. These mutations neither predict an increased susceptibility, nor would indicate someone as being a carrier of a PRX associated myelinopathy. The specification is not enabled for any myelinopathies in general.

On page 9-11, Appellants argue that the specification is enabled for the entire scope of the claims and asserts that the specification provides considerable number of working examples commensurate with the scope and argue that examples 1-3 provide materials and methods to practice the embodiments of the invention, characterization of the PRX gene and mutational analysis in patients. Further argue that Example 8, provides PRX mutations are related to a spectrum of demyelinating neuropathies and assert that there are more than sufficient number and content of working examples in the specification that support the association of PRX mutations with a range of myelinopathies and argue that specification discuss myelinopathies with overlapping phenotypes and the specification provides clear evidence that this group of highly-related diseases having significant phenotypic overlap likely to associate with PRX defects and argue that Appellants are not trying to claim periaxin for a wide range of diseases but those as part of a phenotypically narrow range of myelinopathies. Applicants' arguments are fully considered and are found not persuasive. The instant claims broadly recite diagnosing myelinopathy, which comprises a wide range of myelinopathies and are not limited to the asserted "phenotypically narrow range of myelinopathies". Further "phenotypically narrow range

of myelinopathies" is not defined. Thus it is not clear what diseases belong to this "phenotypically narrow" range of myelinopathies nor which mutations would be predictably diagnostic or associated with this "phenotypically narrow" range. The instant claims require the skilled artisan to assay each possible PRX mutation, to determine which are associated in this undefined "phenotypically narrow range". This leads to further experimentation to determine which mutations are associated with this undefined "phenotypically narrow" range and to further define the scope of applicant's asserted "phenotypically narrow range of myelinopathies".

On page 11 of the appeal brief, Appellants assert that the instant specification states that the association of mutations in PRX with peripheral neuropathy not only identifies another genetic cause for the CMT1 spectrum of myelinopathies but also provides further insights into the molecular mechanisms for theses diseases and is supported by the post-filing references. Appellants also assert that several papers published since the filing of the teaching periaxin alterations that are associated with myelinopathies other than DSN and argue that these publications and the original disclosure teaches that alterations in periaxin are indicative of myelinopathies and thus the instant specification is enabled. Examiner reviewed the published papers provided by the applicants and noted that neither the published papers nor the instant disclosure provide a predictable correlation that all alterations in Prx gene results in myelinopathies in general, any specific myelinopathy or which Prx mutations are periaxin associated myelinopathy mutations. As discussed in the above rejection, Kijima et al. disclose a PRX mutation causing early-onset but slow-progressive X-linked CMT disease, wherein one patient was a female (XX) carries two copies of PRX mutation and other two patients are males (XY) carries a single copy of PRX mutation on X chromosome, thus as expected for X-linked

diseases (Kijima et al. J Hum Genet., Vol. 49, pp. 376-379, 2004). And Takashima et al. teach another study, wherein DSN or CMT affected patients have two mutated alleles where as the unaffected have one mutated allele with no demyelination. The art is silent with regard to a predictable association between any specific alteration or mutation in periaxin and myelinopathy in general. The art does not establish a predictable association that any specific alteration in periaxin is predictably associated with all of the large number of diseases encompassed by the recitation of "myelinopathy".

On page 12 of the appeal brief, Appellants assert that a predictable correlation is not required for enablement of the present invention and assert that appellants fully addressed the issue and argue that the predictable correlation is infact the defect in a periaxin polynucleotide is associated with a myelinopathy, as the claims state, and the myelinopathies are each units of a spectrum of closely-related diseases and assert that the specification provides more than sufficient number of mutations and method to identify additional mutations. Appellants assert that statistically significant data is not required for enablement because a reasonable correlation between periaxin mutations and myelinopathies in general, is provided by the instant specification and assert that examiner is inappropriately requiring statistically significant data for enablement of a claim. These arguments are fully considered and found not persuasive because the mere identification of an alteration does not provide a reasonable correlation with myelinopathies in general. The instant specification provides (example 8) a specific set of mutations in PRX, demonstrates that only a specific type of such mutations are likely to be associated with a specific type of myelinopathy (DSN) but extrapolates that any and all mutations in PRX, including unkwown mutations and mutations which do not necessarily lead to

an altered protein, are associated with any type of myelinopathy. The specification does not support a correlation between any mutation in PRX and any myelinopathy in general. Further, the specification provides in example 8, an association of some specific PRX mutations with peripheral neuropathies. The specification in paragraph (0244) teaches unaffected parents and son of family HOU579 and two sisters and son of the patient HOU418 are heterozygous for PRX mutation. This indicates that the presence of two alleles with specific frameshift mutations is necessary for development of a specific peripheral neuropathy. Thus it is clear that not all mutations of PRX are associated with the broad spectrum of myelinopathies because patients with only a single allele mutation were not affected (see paragraph 0244 on page 66) would not result in myelinopathy in general. The specification fails to teach that all mutations of PRX, irrespective of mutation in a single allele or mutations in two alleles would lead to any type of myelinopathy.

The specification provides working examples that demonstrate that mutations in periaxin are not necessarily disease associated because

(i) only disease association was shown when 2 copies of PRX gene encode a specific protein truncation or frame shift mutation. However, the specification teaches that family members who contained only one copy of the PRX gene with the specific mutation were not affected.

(ii) the specification teaches at page 67, Table 2, that missense mutation occur in both control population as well as unaffected subjects. Therefore the specification shows that a number of mutations found in PRX gene are not disease associated. Thus the specification does not reasonably predict that any mutation in PRX is associated with any myelinopathy.

The specification expressly teaches that certain mutations are not associated with any general or specific myelinopathy therefore it would take a large amount of trail and error analysis for the skilled artisan to determine which mutations are associated and are not associated with the disease. Given the unpredictability with associating PRX mutations and any general or specific nyelinopathy, as shown in the specification, such experimentation is considered undue. As discussed above the unaffected individuals with one copy of the PRX alteration are not afflicted with any myelinopathy and thus the specification fails to establish any reasonable correlation with myelinopathies, specifically or in general, or that the mere fact that an alteration in PRX exists is diagnostic. Further, while some mutations indicate an individual as being a carrier of PRX associated myelinopathy mutation, the specification has provided no guidance as to how one of skill in the art would be able to predict which mutations, from the extremely large number of possible PRX alterations that are known to, exist or that are yet to be detected, would be indicative of diagnostic, susceptibility, or carrier status. As such, the claims are not commensurate in scope with the guidance in the specification or the art, at the time the invention was made.

On page 13-16 of the appeal brief, appellants assert that it is not a requirement to list each and every mutation that results in myelinopathy, given that a representative number of mutations have been provided and assert that Examiner misconstrues the paragraph 0244 of the instant specification and assert that this paragraph teaches absolute classical genetics and does not indicate that PRX mutations are not associated with myelinopathies. Applicants further argue that claims commensurate with the teachings in the specification and the PRX mutations are associated with myelinopathy in general or any of the specific myelinopathies and argue that

they have provided reasonable amount of routine experimentation, sufficient number of periaxin mutations and an appropriate language enabling the invention. These arguments have been thoroughly reviewed. The examiner is not requiring that the specification actually test all of the possible alterations in PRX, but that the specification should provide guidance as to which alterations would be predictably associated. This does not require that the specification should screen each and every possible alteration. As discussed in the previous office action in response to the appellants' arguments filed on August 25, 2004, the specification provides no guidance as to which mutations in PRX would likely result in putative loss of function other than the specific diagnostic alterations taught in the specification, given that lack of guidance in the specification, the skilled artisan would be unable to predictably determine what other alterations would result in loss of function. Thus the specification fails to established any reasonable correlation that any alteration in PRX is associated with myelinopathies in general. With regard to the assertion that the Examiner misconstrues the paragraph 0244, the cited paragraph indicates carriers are not affected even though they carry an alteration in PRX. However claim 1 is broadly drawn to the detection of an alteration in a periaxin, being diagnostic of myelinopathy in general. The examiner agrees that the specification provides that certain specific mutations, while not diagnostic, do indicate an individual as being a carrier of a specific disease associated mutation. However the claims are also broadly drawn to detecting susceptibility to any myelinopathy or being a carrier of a PRX associated myelinopathy. The specification has demonstrated that all PRX mutations are not diagnostic, or indicative of a carrier for any specific myelinopathy or myelinopathy in general. Further, the specification does not teach how one skill in the art could predictably determine which mutations were diagnostic, or indicative that a subject was a carrier

of PRX associated myelinopathy. Further, the specification has not taught which mutations would be predictably associated with a specific myelinopathy. While myelinopathies possess some phenotypic similarities, they also possess differences. However, the specification has not provided guidance as to how or why one mutation is associated with CMT, while another is diagnostic for DSN. To practice the invention as broadly claimed, the skilled artisan would have to carry out studies on each possible mutation to determine if it was or was not diagnostic, indicative of a carrier, susceptibility etc. Such experimentation is related with trail and error analysis with no predictability of out come until effective reduction to practice.

On page 17 of the brief Appellants also argue that the pending claims 1, 35, 43 and new claim 57 require that the myelinopathy results from or is associated with periaxin alteration and therefore these pending claims do not cover myelinopathies resulting from mutations in other polynucleotides and the scope is not so broad as the Examiner contends. These arguments are fully considered and found not persuasive because Examiner notes that not all alterations in periaxin are associated with myelinopathy in general, because as discussed above, the specification provides working examples that demonstrate that all mutations in periaxin are not necessarily disease associated because

(i) only disease association was shown when 2 copies of PRX gene encode a specific protein truncation or frame shift mutation. However, the specification teaches that family members who contained only one copy of the PRX gene with the specific mutation were not affected.

(ii) the specification teaches at page 67, Table 2, that missense mutation occur in both control population as well as unaffected subjects. Therefore the specification shows that a

number of mutations found in PRX gene are not disease associated. Thus the specification does not reasonably predict that any mutation in PRX is associated with any myelinopathy in general.

The specification expressly teaches that certain mutations are not associated with any general or specific myelinopathy therefore it would take a large amount of trail and error analysis for the skilled artisan to determine which mutations are associated and are not associated with the disease. Given the unpredictability with associating PRX mutations and any general or specific nyelinopathy, as shown in the specification, such experimentation is considered undue.

On page 14-18, Appelants assert that Applicants' argue that the declaration filed on December 18, 2003 discusses the issues and concerns raised by the Examiner regarding the data in Table-2 of the specification and request the examiner to reconsider the declaration. Applicants' arguments have been fully considered. The declaration filed on December, 18, 2003 has been reconsidered in light of the response's traversal regarding Table 2, however neither the arguments in the response nor the declaration were persuasive. The declaration indicates that the instant specification discloses several mutations in PRX cause a broad spectrum of demyelinating neuropathies, that include CMT1 and DSN as show in specific paragraphs (0244 and 0260) of the specification. The declaration also discloses that the specification teaches (at least in examples 2-8 as cited in paragraphs 0062, 0242, 0244, 0246, 0247, 0260, 0261, 0268 and 0273) a skilled artisan to recognize and assess a difference in a polymorphism and a disease-causing mutation. With regard to the data in Table 2, examiner notes that Table-2 shows PRX mutations in unaffected controls. The specification does not teach if patients had one copy of mutation, or if they were homozygous or compound heterozygous for other mutations in periaxin. It is clear from the teachings in Table-2, that the mere presence of an alteration in

periaxin such as a substitution or deletion is not diagnostic for myelinopathy. Further, with regard to the 2145T-> A and 274Δ C mutation in claim 36, and the R196X, C715X, or R82FSX96, the specification has provided no data as to whether these mutations are even associated with myelinopathy. Since the specification has not identified any specific critical amino acid alteration, it is further unclear whether these mutations or any specific mutation will have a significant affect or not. With regard to the heterozygous carriers carrying a PRX mutant allele, the specification fails to establish that the mere presence of an alteration in PRX as claimed broadly in the new claims 51-61 would result in carriers of disease causing PRX mutant alleles. Applicants' arguments with regard to the differences in a polymorphism vs a disease-causing mutations are fully considered. However, based on these arguments it is clear that each and every mutation or alteration in PRX would not be a disease-causing mutation. Thus it further clarifies that the mere detection of an alteration is not diagnostic yet the claims broadly encompass such mutations or alterations. The declaration asserts at page 3, that one of skill in the art would know how to discern between a polymorphism and a disease causing mutation, because if an alteration is a polymorphism it is not identified controls and /or does not segregate with the disease phenotype. This argument has been thoroughly reviewed but was found unpersuasive. Such assertions highlight the need that the skilled artisan would require experimentation to determine whether an alteration was diagnostic or associated with myelinopathies – either prominent sensory neuropathies or to specific meylinopathies. However, the claims are not drawn to determining whether an alteration is diagnostic or disease associated, but to methods of diagnosing or determining increased susceptibility or a carrier status merely based on detection of an alteration. However, as exemplified by the specification all alterations

in Prx are not predictably correlated with myelinopathies, including prominent sensory neuropathies.

On page 18 of the appeal brief, Appellants' argue that Examiner has not addressed why the declaration is dismissed and assert the it is unclear why the Examiner does not recognize the art by others that recognized the predictable correlation and argue that Appellants teachings are sufficient to provide a predictable correlation and assert that the examiner can not dismiss a declaration without adequate explanation of why the declaration failed to over come the rejections. Appellants' arguments are fully considered and found unpersuasive because as discussed above, the declaration indicates that the instant specification discloses several mutations in PRX cause a broad spectrum of demyelinating neuropathies, that include CMT1 and DSN as show in specific paragraphs (0244 and 0260) of the specification. The declaration also discloses that the specification teaches (at least in examples 2-8 as cited in paragraphs 0062, 0242, 0244, 0246, 0247, 0260, 0261, 0268 and 0273) a skilled artisan to recognize and assess a difference in a polymorphism and a disease-causing mutation. With regard to the data in Table 2, examiner notes that table-2 shows PRX mutations in unaffected controls. The specification does not teach if patients had one copy of mutation, or if they were homozygous or compound heterozygous for other mutations in periaxin. It is clear from the teachings in Table-2 or the declaration, that the mere presence of an alteration in periaxin such as a substitution or deletion is not diagnostic for myelinopathy in general. Further, with regard to the 2145T-> A and 274Δ C mutation in claim 36, and the R196X, C715X, or R82FSX96, the specification has provided no data as to whether these mutations are even associated with myelinopathy. Since the specification has not identified any specific critical amino acid alteration, it is further unclear

whether these mutations or any specific mutation will have a significant affect or not. With regard to the heterozygous carriers carrying a PRX mutant allele, the specification fails to establish that the mere presence of an alteration in PRX as claimed broadly in the new claims 51-61 would result in carriers of disease causing PRX mutant alleles. The declaration asserts at page 3, that one of skill in the art would know how to discern between a polymorphism and a disease causing mutation, because if an alteration is a polymorphism it is not identified controls and /or does not segregate with the disease phenotype. This argument has been thoroughly reviewed but was found unpersuasive. Such assertions highlight the need that the skilled artisan would require experimentation to determine whether an alteration was diagnostic or associated with myelinopathies – either prominent sensory neuropathies or to specific meylinopathies. However, the claims are not drawn to determining whether an alteration is diagnostic or disease associated, but to methods of diagnosing or determining increased susceptibility or a carrier status merely based on detection of an alteration. However, as exemplified by the specification all alterations in PRX are not predictably correlated with myelinopathies, including prominent sensory neuropathies.

On page 19 of the appeal brief, Appellants argue that, that the specification has provided more than sufficient number of working examples and assert that undue experimentation is not required, and a considerable amount of experimentation is permissible, as stated in the declaration by Dr. Lupski, a skilled artisan would be able to distinguish between the diseases-causing mutations and mutation which confer carrier status and assert the specification is enabled and the claims commensurate with the scope of the instant specification. Appellants' assertions are fully considered, but were found not persuasive. The specification does not provide a

reasonable amount of guidance and direction in which the experimentation should proceed because the specification does not teach which mutations in PRX would predictably be diagnostic or have any effect on the activity or function of periaxin. The specification fails to establish any general diagnsotic correlation with myelinopathies in general or prominent sensory neuropathy. To practice the invention as broadly as it is claimed the skilled artisan would be required to actually assess each and every variant to detect if it was diagnostic for myelinopathy in general or any specific myelinopathy. The specification shows that some mutations are associated and some are not, but does not provide any guidance as to which mutations would be predictably associated. Without such guidance one skilled in the art would have to screen each position to determine if a mutation is disease-causing or disease associated mutation vs mutation not associated with disease, outcome of such experimentation is unpredictable. Further the specification provides no guidance as to which mutations are diagnostic or associated with myelinopathies, or have any effect on the function of periaxin, such experimentation would be replete with trial and error analysis with no ability to predict outcome. Such experimentation is not routine, but requires inventive effort to actually determine which mutations fall within the scope of the claimed invention. In the instant case, the specification does not provide any guidance or direction as to which mutations would have a significant effect or not nor does it provide guidance as to which direction the experimentation should proceed, other than to actually asses each alteration. Without such experimentation, there is no way to actually predict which mutations would fall within the scope of the claimed invention. Such experimentation is considered undue.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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August 17, 2005

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